



Caregiver subjective and physiological markers of stress and patient heart failure severity in family care dyads

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ABSTRACT

Greater family caregiver exposure to uncontrolled patient symptoms is predictive of greater caregiver psychological and physiological stress in dementia and other chronic illnesses, but these phenomena have not been well-studied in heart failure (HF) – a disease with high symptom burden. The purpose of this study was to test the hypothesis that worse patient functional status (as reflected by increasing HF symptoms) would be associated with elevated psychological and physiological stress for the caregiver. This was a secondary analysis of data from 125 HF caregivers in the Caregiver Opportunities for Optimizing Lifestyle (COOL) study. Psychological stress was measured on four dimensions: care-related strain/burden (Oberst Caregiving Burden Scale), depression (Center for Epidemiological Studies Depression Scale), anxiety (State-Trait Anxiety Index), and general stress (Perceived Stress Scale). Physiological stress was measured by markers of HPA axis function (elevated cortisol awakening response [CAR]), endothelial dysfunction (increased PAI-1), and inflammation (increased IL-6, hsCRP). HF patient functional status was quantified by caregiver assessment of New York Heart Association (NYHA) Class. Generalized linear models were used to test associations between patient NYHA Class and stress (one model per indicator). NYHA Class (ordinal) was backwards difference coded in each model to examine caregiver stress in relation to increasing levels of HF severity. Caregivers were mostly female and in their mid-fifties, with a slight majority of the sample being African American and the patient's spouse. Overall, patient functional status was associated with greater caregiver psychological and physiological stress. In terms of psychological stress, higher NYHA Class was significantly associated with greater caregiver anxiety and general stress, but not with caregiver burden or depression. In terms of physiological stress, higher NYHA Class was associated with elevated markers in all models (elevated CAR and higher IL-6, hsCRP, and PAI-1). Across models, most associations between NYHA Class and stress were present at relatively early stages of functional limitation (i.e. Class II), while others emerged when functional limitations became more severe. To inform timing and mechanisms for much-needed caregiver interventions, research is needed to determine which aspects of HF symptomatology are most stressful for caregivers across the HF trajectory.

1. Introduction

Chronic heart failure is a complex, progressive syndrome that arises when the heart can no longer adequately fill or eject blood to meet the

body's circulatory needs (Yancy et al., 2013). Over 6.2 million adults in the US have HF, and this number is projected to increase to >8 million within the next 10 years (Heidenreich et al., 2013; Virani et al., 2020). The majority of incident heart failure develops as a direct or indirect

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consequence of highly prevalent cardiometabolic diseases, such as hypertension, coronary heart disease, and diabetes, as well as common risk factors related to lifestyle behaviors, such as obesity and smoking, and advancing age (Arnett et al., 2019; Strait and Lakatta, 2012; Virani et al., 2020). As a result, HF is the fastest growing cardiovascular disease in the country and poses a substantial risk to individual and public health (Heidenreich et al., 2013). HF is responsible for significant morbidity and mortality in patients, who experience chronic and distressing symptoms, clinical trajectories that are characterized by high levels of uncertainty, frequent hospitalization and re-hospitalization, and limited treatment options at advanced stages of disease (Allen et al., 2012). Furthermore, due to progressive functional limitations and the complexities of home management, many HF patients must rely on family members or other close friends, neighbors, or community members (i.e. caregivers) to provide unpaid support to manage their illness (Kitko et al., 2020). Although comparatively less research has been conducted on the experience of caring for a person with HF as opposed to caregiving in other chronic conditions (e.g. dementia, cancer), what is known suggests that caring for a person with HF poses substantial physical, psychological, and financial risks to individuals and families (Dunbar et al., 2018; Kitko et al., 2020).

For persons with HF and their caregivers, the day-to-day experience of managing the condition at the earliest stages involves routine adherence to medications and healthy lifestyle behaviors (Riegel et al., 2015). As the disease advances, however, the experience of HF becomes characterized by continuous management of progressive and pervasive symptoms (e.g. dyspnea, fatigue, edema, insomnia) that severely compromise quality of life (Lum et al., 2016; Riegel et al., 2015). At home, daily monitoring for changes in symptoms and timely response to symptom exacerbations are difficult but essential components of patient and caregiver management of disease, as providers' clinical management is supported by patients' and families' evaluations of symptoms and notifications when symptoms worsen (Buck et al., 2015; Riegel et al., 2015; Yancy et al., 2013). Importantly, the primary clinical classification used by providers to characterize HF disease severity – New York Heart Association functional class – is largely determined by patient severity of symptoms (Criteria Committee of the NYHA, 1994). However, while HF symptoms are central to the daily management of disease and substantially increase the complexity of caregiving, very little research has been done on the experience of HF symptoms from the perspective of the caregiver.

In the broader literature related to chronic illness caregiving, there is evidence that greater family caregiver exposure to distressing patient symptoms is predictive of greater caregiver psychological and physiological stress (Schulz et al., 2020). While this effect has also been observed in HF caregivers in terms of subjectively-reported psychological stress (Bidwell et al., 2017), research in this area is limited, and to our knowledge no studies have examined caregiver physiological stress in relation to HF patient symptoms. This gap prevents researchers from understanding which points in the trajectory of HF caregiving may be most difficult for caregivers, or carry the most risk to physical or mental health. Thus, the purpose of the present study was to test the hypothesis that worse patient functional status (as reflected by increasing HF symptoms) would be associated with elevated stress for the caregiver. Specifically, we hypothesized that caregiver experience of increasing patient symptoms would be significantly associated with: (1) elevated measures of caregiver psychological stress (caregiver strain/burden, depression, anxiety, general stress), and (2) elevated indicators of caregiver physiological stress (HPA axis hyperactivity, inflammation, endothelial dysfunction). We chose these biomarkers due to the evidence implicating them in the pathways from life stress to the development of deleterious mental or physical health outcomes (Chida and Steptoe, 2009; Hostinar et al., 2015). The HPA axis is one of the body's primary stress-response systems, whose primary output is the hormone cortisol. The cortisol awakening response (CAR) has been previously linked to both psychosocial stress exposure (Chida and Steptoe, 2009),

and to mental health outcomes; for example, a recent meta-analysis has linked increased CAR to depression (Boggero et al., 2017). Proteins involved in orchestrating inflammation, such as C-reactive protein and interleukin-6, have also been shown to be elevated in individuals experiencing high levels of chronic psychosocial stress (Hostinar et al., 2015) and to predict cardiovascular morbidity and mortality in a dose-response manner (Ridker, 2007). Endothelial dysfunction is increasingly recognized as an important pathway between exposure to psychosocial stress and the development of atherosclerosis, and plasminogen activator inhibitor-1 (PAI-1) is a marker of endothelial dysfunction that plays a critical role in multiple preclinical and clinical conditions (Cesari et al., 2010).

2. Material and methods

2.1. Overall study design

This was a secondary analysis of data from the Caregiver Opportunities for Optimizing Lifestyles in Heart Failure study (COOL-HF, ClinicalTrials.gov identifier NCT01188070), a randomized-controlled trial of psychoeducational and exercise interventions to improve caregiver physical function and reduce caregiving-related strain. The design of the COOL-HF study and its main results have been published previously (Gary et al., 2018). In short, HF caregivers were randomized into three intervention groups: (1) attention control, (2) psychoeducation on self-care and coping, or (3) psychoeducation combined with a low-impact aerobic and resistance exercise program. Data were collected prior to randomization (baseline) and at six months. For the present study (secondary analysis), only participants' baseline data were utilized.

2.2. Participants

One hundred twenty-seven participants were recruited from three sources: (1) in-person at several outpatient HF clinics of a large, urban university medical center (the coordinating institution), (2) via mail from a regional research repository of HF patients and families willing to be contacted for research (Marti et al., 2013), and (3) outpatient cardiology clinics of two urban health systems. All recruitment sites were located in the Southeastern United States, as was the coordinating institution. "Caregiver" was defined as a spouse, partner, or other adult family member of a HF patient, either living in the same house or in contact with the patient in a caregiving capacity at least 4 times per week for at least one hour or more each time. To be included in the study, caregivers had to be 21 years of age or older, fluent in English, physically capable of engaging in the exercise intervention (walking and upper body strength training), and willing and able to provide informed consent. Multiple caregivers of the same patient were not included. Caregivers were also excluded if they were already physically active (regularly engaged in moderately strenuous exercise ≥ 3 more times per week for ≥ 30 min), current smoker, currently taking corticosteroids, unable to participate in the exercise intervention due to physical or medical condition(s), failed the baseline treadmill test (demonstrated ischemia or inappropriate blood pressure changes), had severe untreated psychiatric comorbidity or cognitive impairment, or presented with an acute inflammatory event at the time of baseline testing. The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki, and all study participants provided written informed consent.

For this secondary analysis, all participants who provided baseline data evaluating patient symptoms were included ($n = 125$). Given this predetermined sample size of 125, with power = 0.80 and alpha = 0.05, the minimum detectable effect for the hypothesized correlation between caregiver stress and patient symptoms (one-tailed) is 0.22 (GPower 3.1; post-hoc power analysis). Limited research has examined patient HF symptoms in relationship to caregiver stress, typically with sample sizes

well under 100 participants (Bidwell et al., 2017). In these studies, the direction of this relationship has been consistent, and the minimum detectable effect of $r = 0.22$ for the present study is well within the range of observed effects from prior studies.

2.3. Procedures

Procedures for the collection of baseline data were as follows. After initial screening and identification at the recruitment sites, a research nurse met with potential participants to: (1) complete eligibility screening, (2) obtain informed consent, (3) collect basic demographic and clinical data via interview, (4) provide training in the collection of salivary cortisol samples, (5) distribute the baseline packet of study questionnaires, and (6) schedule the first study visit at the participant's convenience. The first study visit was conducted at the coordinating center's translational research clinic. At this visit, research staff reviewed the baseline packet of study questionnaires with participants, obtained the salivary cortisol samples which participants had collected at home, conducted a brief history and physical exam (which included the collection of clinical and anthropometric data), and collected blood for serum biomarkers. Only after these baseline data collection procedures were completed did randomization to study groups and subsequent intervention occur. Data for all study time points was de-identified and stored on secured drives, and only the data required for the present study (baseline time point data) was retrieved for this secondary analysis.

2.4. Assessments of caregiver psychological stress

2.4.1. Caregiving burden

Caregiving burden was measured using the Oberst Caregiving Burden Scale (OCBS) (Bakas et al., 2004; Oberst et al., 1989). The OCBS is a 30-item instrument that quantifies care burden in terms of time spent on common physical and emotional caregiving tasks (time subscale, 15 items) and caregiver perceptions of difficulty associated with those tasks (difficulty subscale, 15 items). The difficulty, rather than the time, subscale was utilized in the modeling for the present study. As a subjective evaluation of challenges related to caregiving, it is better aligned with our overarching construct of subjective caregiving stress than time spent caregiving, which is often considered to be an objective dimension of caregiving burden (Bastawrous, 2013). On the difficulty scale, respondents evaluate the difficulty of each caregiving item (e.g. "Medical or nursing treatments [giving medications, skin care, dressings, etc.]," "Emotional support, 'being there' for the patient") on a 5-point Likert scale, ranging from 1, "Not Difficult," to 5, "Extremely Difficult." Individual item scores for the difficulty subscale are summed to produce a total score with a possible range of 15–75. Higher total scores indicate greater caregiving strain/burden. The time scale was used descriptively. On the time scale, respondents evaluate the time spent on each caregiving task, again on a 5-point Likert scale, ranging from 1, "No Time," to 5, "A Great Amount of Time." Scores are summed to produce a total score with a possible range of 15–75, with higher scores indicating greater time spent caregiving. Evidence of validity and reliability have been demonstrated in previous studies of caregiving in stroke and HF (Bakas et al., 2004; Pressler et al., 2009). Cronbach's alpha for the OCBS difficulty subscale in the present study was excellent: 0.94.

2.4.2. Depression

Caregiver depression was measured using the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977). The CES-D is a 20-item instrument designed to quantify the burden of depressive symptoms in community-dwelling participants. Each item presents a feeling or behavior (e.g. "I felt that everything I did was an effort," "I enjoyed life"), and respondents rate the frequency with which they experience that feeling/behavior in a given week. Responses are on a

4-point Likert scale, ranging from 0, "Rarely or None of the Time (Less than 1 Day)," to 3, "Most or All of the Time (5–7 Days)." Some items are reverse-coded, then all item scores are summed to produce a total score with a possible range of 0–60. Higher total scores indicate greater depressive symptoms. Evidence of validity and reliability have been established in the general population in the United States (Radloff, 1977), and have also been demonstrated in studies of caregiving in dementia and HF (Saunders, 2009; Ying et al., 2019). Cronbach's alpha for the CES-D in the present study was excellent: 0.89.

2.4.3. Anxiety

Anxiety was measured using the State Trait Anxiety Inventory (STAI) (Spielberger, 1983). The STAI is a widely-used, 40-item instrument that quantifies anxiety both as a transitory emotional state (state subscale, 20 items) and as a stable personality trait (trait subscale, 20 items). The state subscale was utilized in this study. Each item presents respondents with a different feeling (e.g. "I feel calm," "I am tense"), to which the respondent rates the degree to which that feeling represents their current state. Responses are on a 4-point Likert scale, ranging from 1, "Not at All," to 4, "Very Much So." Some item scores are reverse-coded, then all items are summed to produce a total score with a possible range of 20–80. Evidence of reliability and validity have been established in samples of community-dwelling and clinical populations (Spielberger, 1983), and reliability has been demonstrated in caregiving studies of dementia and other chronic illnesses (Vitaliano et al., 2005). Cronbach's alpha for the state subscale of the STAI in the present study was excellent: 0.96.

2.4.4. General stress

General stress was measured using the Perceived Stress Scale (PSS) (Cohen et al., 1983). The Perceived Stress Scale is designed to quantify participants' stress appraisal in response to life situations. The original instrument consisted of 14-items, but the 10-item instrument is commonly used because of minor advantages in length and psychometric performance. The 10-item version of the PSS was utilized in this study. Each item prompts respondents to evaluate how frequently they have had a given feeling or thought within the past month (e.g. "how often have you felt that you were unable to control the important things in your life?," "how often have you felt difficulties were piling up so high that you could not overcome them?"). Responses are on a 5-point Likert scale, ranging from 0, "Never," to 4, "Very Often." Some item scores are reverse coded, then all items are summed to produce a total score with a possible range of 0–40. Evidence of reliability and validity have been established in the general population in the United States (Cohen and Williamson, 1988), as well as in prior work with caregivers of patients with HF (Schwarz and Dunphy, 2003). The Cronbach's alpha for the PSS in the present study was excellent: 0.91.

2.5. Assessment of caregiver physiological stress

2.5.1. Serum biomarkers of inflammation and endothelial dysfunction

Caregiver inflammation was quantified using two serum biomarkers: the cytokine interleukin-6 (IL-6) and C-reactive protein (CRP), an acute-phase protein. Both IL-6 and CRP are frequently studied as markers of inflammation in research on physiologic caregiving stress, with higher levels considered indicative of greater inflammation (Allen et al., 2017; Roth et al., 2019). Furthermore, they both predict cardiovascular morbidity and mortality in large population-based studies (Ridker, 2007). Caregiver endothelial dysfunction was quantified by increased expression of serum plasminogen activator inhibitor-1 (PAI-1). Endothelial dysfunction and other similar cardiovascular markers are less commonly studied in caregivers, but PAI-1 has been examined as a marker of hypercoagulability both independently and in concert with other markers (Allen et al., 2017; Park et al., 2018). After overnight fasting, blood collection was done via standard venipuncture by a research phlebotomist, and samples were immediately placed on ice

prior to being centrifuged at 3000 rpm for 15 min at 4 °C. Once processed, samples were aliquoted and stored at –80 °C until assayed. IL-6 and PAI-1 were assayed in duplicate by ELISA according to manufacturer's specifications (enzyme-linked immunosorbent assays; R&D Systems, Minneapolis, MN, USA). Inter- and intra-assay variability for IL-6 were reliably <10%, and lower limit of detection was 0.04 pg/mL. Inter- and intra-assay variability for PAI-1 were 7.4% and 4.9%, respectively, with 0.3 as the lower limit of detection. High sensitivity CRP was analyzed by immunoturbidimetric assay on the Beckman 750 Chemistry Autoanalyzer using reagents and calibrators from Sekisui Diagnostics. Inter- and intra-assay variability for hsCRP were 3.1% and 2.1%, respectively.

2.5.2. Salivary cortisol biomarker of HPA-axis function

HPA-axis function was measured using salivary cortisol awakening response (CAR), a measure of HPA-axis activity during the 30–45 min immediately after waking. An elevated proportional increase in CAR indicates heightened HPA-axis activity, and has been significantly associated with chronic life stress (Chida and Steptoe, 2009). Both CAR and other salivary cortisol measures of HPA-axis activity have been used as measures of physiologic stress in caregiving research (Allen et al., 2017; Park et al., 2018). Participants were provided with detailed instructions for saliva collection, modeled after instructions given to participants in a previous large study of HPA-axis dysregulation and stress in a diverse sample (Matthews et al., 2006). Participants self-collected saliva over two consecutive days using Salivettes (SAR-STEDT; Numbrecht, Germany) at awakening and 30 min after awakening. Participants stored the samples in a provided sealed container in their home freezer and delivered them in a provided portable cooler on ice to the study laboratory at the time of their baseline visit. Each sample was assayed in duplicate using a commercially available ELISA kit (Salimetrics; Carlsbad, CA), which has a sensitivity of 0.007 µg/dl and intra- and inter-assay coefficients of variation of <8% and <11%, respectively. CAR was calculated as the percent change between the average waking values and the average 30 min post-waking values, averaged across the two days of measurement.

2.6. Assessment of patient symptoms

Patient HF functional status as demonstrated by HF symptom severity was quantified by caregiver assessment of the patient's New York Heart Association (NYHA) functional class (Criteria Committee of the NYHA, 1994). In contrast to a number of other chronic illnesses in which functional decline is characterized primarily by progressive loss of independence in basic/instrumental activities of daily living, functional status in HF is characterized by progressive increase in symptoms (e.g. shortness of breath, fatigue). NYHA functional classification is a subjective assessment of a patient's HF severity based on symptom burden in response to physical activity. It is the current clinical standard for subjective assessment of HF disease severity and progression, and is also used to guide evidence-based therapies (Yancy et al., 2017, 2013). NYHA Class is assessed with a single-item that has four response categories separating patients into Class I, II, III, or IV, with higher classes indicating greater HF symptom severity. Class I patients have no HF symptoms and no limitations to their physical activity, Class II patients have HF symptoms with ordinary physical activity and slight limitations to their physical activity, Class III patients have HF symptoms with less-than-ordinary physical activity and have marked limitations to their physical activity, and Class IV patients have HF symptoms at rest and are unable to do any physical activity without discomfort. In addition to its clinical use, NYHA class has been used in a number of studies of HF caregiving to examine or control for disease severity in relation to caregiver stress (Bidwell et al., 2017).

2.7. Covariates

All models controlled for common sociodemographic and health-related confounders of stress in caregivers: age, race, sex, education, comorbidity, caregiving relationship type, and cohabitation with the care recipient (Schulz et al., 2020). Comorbidities were measured using the Charlson Comorbidity Index (Charlson et al., 1987). For all physiological stress models, four known confounders of inflammatory stress biomarkers were added based on guidance from O'Connor et al. (2009) regarding biobehavioral control variable selection in studies of inflammation: (1) use of aspirin, antihypertensive, or statin medication, (2) use of selective serotonin reuptake inhibitors, (3) adiposity (as measured by waist-hip ratio), and (4) sleep quality. Medications were obtained by self-report, and waist-hip ratio measurement was obtained by trained research staff. Due to sample size and concerns of oversaturating models with too many covariates, use of aspirin, antihypertensives, and statins were combined into one variable that reflects participants' use of any one of those cardiovascular medications. Sleep disturbances were measured using the Pittsburgh Sleep Quality Index (Buysse et al., 1989). Inflammatory marker controls were retained in both the endothelial dysfunction and HPA dysfunction models, given that similar associations with these variables have been observed in studies with those markers (Cesari et al., 2010; Bjorntorp and Rosmond, 2000; Granger et al., 2009). In terms of endothelial dysfunction, PAI-1, similar to inflammatory markers, is also associated with adiposity and cardiovascular and serotonergic medications (Cesari et al., 2010). Smoking and high levels of physical activity are also common correlates of PAI-1 levels (Cesari et al., 2010), but were not necessary to include as controls in the present study given that none of the participants were smokers, and only sedentary caregivers were enrolled. In terms of HPA dysfunction, salivary cortisol is also confounded by cardiovascular and serotonergic medications, adiposity, and sleep disturbances (Bjorntorp and Rosmond, 2000; Granger et al., 2009; Law et al., 2013). Pain was also added to the HPA-dysfunction model, given its association with cortisol levels (Fabian et al., 2009). Pain was measured using the Bodily Pain scale of the Short Form-36 (Ware, 2000). A correlation table including the major study variables and covariates is provided in Appendix 1. Model covariates were initially proposed to the study team by the lead author, then discussed and revised based on the team's expertise and suggestions. Final decisions on all models were made by the lead author. Given multiple covariates, all models were examined post hoc for collinearity of predictors, with no evidence of multicollinearity in any of the models (no variance inflation factors >2).

2.8. Analysis

Standard descriptive statistics (means and standard deviations, proportions) were used to characterize the sample. Generalized linear models were fit for each dependent variable (i.e. one model for each psychological and physiological stress variable). Gaussian identity and gaussian log models were used for cytokine and CAR models, respectively, and subjective stress indicators were modeled using the gamma probability distribution. Patient HF functional status related to symptom severity (caregiver-assessed NYHA Class, primary independent variable) was backwards difference coded to examine the relationship between caregiver stress (dependent variable) with increasing levels of NYHA Class. Backwards difference coding (also known as reverse Helmert coding) is particularly useful when examining effects associated with increasing levels of an ordinal variable, as each level of the ordinal variable is coded for comparison to the mean of the prior level or combined levels (Chen et al., 2003). In the present analysis, this is operationalized in the models as two dummy variables: (1) Class II versus Class I (referent), and (2) Class III/IV versus Class I/II (referent). Class III/IV were combined due to the comparatively smaller proportion of caregivers of Class IV patients in the sample. Prior to modeling, serum markers (IL-6, hsCRP, PAI-1) were natural log transformed, and CAR

was dichotomized based on a cutoff for elevated stress response (>75% increase in cortisol 30 min after waking; Hellhammer et al., 2009). Serum markers were also examined for outliers, and extreme values were identified in the data for inflammatory markers IL-6 and hsCRP (two values >10 pg/mL for IL-6, three values >15 mg/L for hsCRP). Sensitivity analyses including and excluding these extreme outliers for IL-6 and hsCRP yielded the same conclusions. The analyses reported in the results and tables exclude these extreme values. All analyses were completed using StataMP version 16 (College Station, TX).

3. Results

3.1. Sample characteristics

The sociodemographic characteristics of the sample (n = 125) are presented in Table 1. The majority of participants were female and in their mid-fifties, and just over half identified as African American. Most caregivers were the patient’s spouse, and the second most common caregiving relationship type was parent-child (i.e., adult children of the HF patient); the remaining caregivers were other kith or kin (e.g. friends or family members who lived close by). On average, caregivers reported spending a moderate amount of time on caregiving activities. Approximately one quarter of caregivers assessed the HF patient’s functional status as NYHA Class I (asymptomatic), and one quarter assessed patient functional status as NYHA Class II (mild symptoms). Most of the remaining half of caregivers assessed patient functional status as NYHA Class III (moderate symptoms), with a small proportion assessing patient HF status as NYHA Class IV (severe symptoms).

The distribution of caregiver psychological and physiological stress variables by patient NYHA Class is presented in Figs. 1 and 2, respectively. For the psychological stress variables overall, the sample means and standard deviations were as follows: caregiving burden 33.3 ± 14.4 (range 18–75), depression 15.1 ± 10.2 (range 0–46), anxiety 40.9 ± 14.8 (range 20–70), and general stress 17.1 ± 7.3 (range 3–36). For the physiologic stress variables overall, the sample means and standard

Table 1
Sample characteristics (n = 125).

Characteristic	Mean ± SD or n (%)	Observed range
Age (years)	55.4 ± 11.5	25–80
Gender (female)	115 (92%)	
Race		
African American	72 (57.6%)	
Asian	2 (1.6%)	
White	51 (40.8%)	
Hispanic/Latinx ethnicity	3 (2.4%)	
Education (highest completed)		
High School	21 (16.8%)	
Technical/Vocational	17 (13.6%)	
College	63 (50.4%)	
Post-Graduate	24 (19.2%)	
Caregiving Relationship Type		
Spouse	68 (55.3%)	
Child	30 (24.4%)	
Other	25(20.3%)	
Lives with Care Recipient	105 (84%)	
Time Spent Caregiving ^a	44.90 ± 12.18	22–75
NYHA Class of Care Recipient		
Class I (asymptomatic)	32 (25.6%)	
Class II (mild symptoms)	31 (24.8%)	
Class III (marked symptoms)	47 (37.6%)	
Class IV (severe symptoms)	15 (12.0%)	
Caregiver Health		
Charlson Comorbidity Index Score	0.65 ± 1.18	0–8
Adiposity (waist-hip ratio)	0.87 ± 0.07	0.71–1.15
Sleep Quality ^b	8.36 ± 4.20	0–19
Pain ^c	48.53 ± 9.90	19.86–62.12

^a Oberst Caregiving Burden Scale – Time Score; possible range 15–75.

^b Pittsburgh Sleep Quality Index; possible range 0–21.

^c Short Form-36 – Bodily Pain; possible range 0–100.

deviations for the raw values of serum biomarkers were as follows: IL-6 2.12 ± 1.71 pg/mL (median 1.47, interquartile range [IQR] 1.15–2.39, range 0.27–9.03), hsCRP 3.25 ± 3.33 mg/L (median 1.91, IQR 1.06–3.60, range 0.12–14.50), and PAI-1 3.80 ± 2.86 ng/mL (median 2.71, IQR 1.86–5.14, range 0.54–16.93). The sample mean and standard deviation for the percent increase in salivary cortisol from waking to 30 min was 62.3 ± 94.1 (median 31.9, IQR –8.6 to 114.8, range –74.3 to 325.8).

3.2. Caregiver psychological stress by patient heart failure functional class

The models testing the relationship between caregiver psychological stress and patient NYHA Class are presented in Table 2. Higher patient functional class (i.e. increasing HF symptom severity) was not significantly associated with greater caregiver burden or caregiver depression. However, higher patient functional class (worse symptom severity) was significantly associated with greater caregiver anxiety and general stress, although at differing levels of patient functional class. In terms of anxiety, caring for a patient with mild HF symptoms (Class II) versus no symptoms (Class I) was significantly associated with greater caregiver anxiety. No further significant elevations (or decreases) in caregiver anxiety were observed in relation to caring for a patient with more severe symptoms (i.e. caregiver anxiety in relation to caring for a patient with more severe symptoms [Class III/IV] was not significantly different than the level of anxiety associated with caring for a Class I or II patient). In terms of general stress, caring for a patient with mild HF symptoms (Class II) versus no symptoms (Class I) was not significantly associated with stress. However, caring for a patient with more severe symptoms (Class III/IV) was significantly associated with greater caregiver general stress.

3.3. Caregiver physiological stress by patient heart failure functional class

The models testing the relationship between caregiver physiological stress and patient NYHA Class are presented in Table 3. Higher patient functional class (i.e. greater HF symptom severity) was significantly associated with all markers of caregiver physiological stress, although at differing levels of patient functional class. For caregiver inflammation (IL-6, hsCRP) and endothelial dysfunction (PAI-1), caring for a patient with mild HF symptoms (Class II) versus no symptoms (Class I) was significantly associated with elevated caregiver physiological stress. No further significant elevations (or decreases) in these markers were observed in relation to caring for a patient with more severe symptoms (i.e. caregiver inflammation and endothelial dysfunction in relation to caring for a patient with more severe symptoms [Class III/IV] was not significantly different than the level of inflammation/endothelial dysfunction associated with caring for a Class I or II patient). In terms of HPA-axis dysfunction (CAR >75%), caring for a patient with mild HF symptoms (Class II) versus no symptoms (Class I) was not significantly associated with elevated CAR. However, caring for a patient with more severe symptoms (Class III/IV) was significantly associated with elevated CAR.

4. Discussion

In this study of psychological and physiological stress in a racially diverse sample of caregivers of persons with HF, we found that care recipient HF functional status (as characterized by caregiver-assessed patient symptom severity) was associated with most of our indicators of greater caregiver psychological and physiological stress. Across models, most associations between patient NYHA Class and caregiver stress were present at relatively early stages of HF symptom-related functional limitations (i.e. Class II), while others emerged when functional limitations became more severe. Here, we discuss our findings related to caregiver psychological and physiological stress, consider potential reasons why some commonly-measured indicators of caregiver

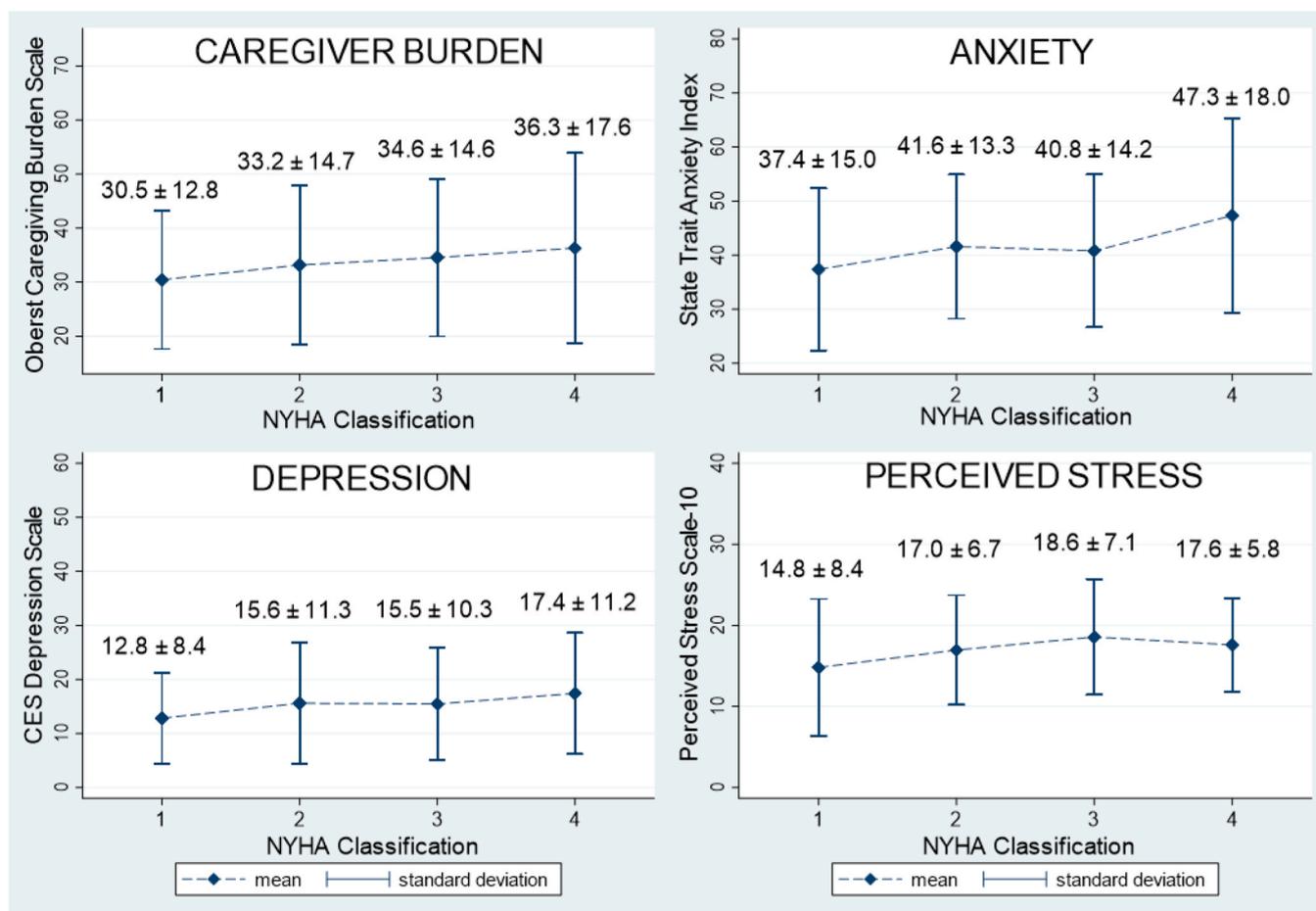


Fig. 1. Caregiver psychological stress variables by caregiver-assessment of the care recipient’s heart failure functional classification (higher NYHA Class indicates greater severity of care recipient heart failure symptoms). Abbreviations: CES, Center for Epidemiological Studies; NYHA, New York Heart Association.

psychological stress were not significantly associated with patient HF severity in the present study, and discuss novel contributions and potential implications.

Our first hypothesis – that greater severity of patient symptoms would be associated with elevated caregiver psychological stress – was somewhat inconsistently supported (i.e. greater severity of patient symptoms was not associated with greater caregiver burden or depression, but was associated with greater caregiver anxiety and general stress). Across studies of general chronic illness caregiving, elevated patient symptoms are frequently associated with caregiver burden and other indicators of psychological distress (Schulz et al., 2020). While we did find significant positive relationships between increasing HF symptoms and caregiver anxiety and general stress, we found no relationship with caregiver burden or depression. The lack of relationship between symptoms and caregiver burden was surprising, given that across studies of HF caregivers, caregiver burden has been fairly consistently associated with increasing patient HF severity despite relatively small sample sizes (Bidwell et al., 2017).

It is possible that our divergent finding may be explained, in part, by measurement effects. Although prior studies examining HF severity and caregiver burden have commonly used NYHA Class as a measure of symptom severity related to HF functional decline (Bidwell et al., 2017), it is a single-item, 4-level instrument, meaning it is less robust to measurement error and has limited precision. Further, in this study, HF functional decline was measured using caregivers’ assessments of NYHA Class, rather than patients’ or clinicians’ assessments. Although there is precedent for using caregiver ratings of HF patient symptoms (Saunders, 2008), caregiver and patient symptom ratings can be incongruent (Lee

et al., 2017). Additionally, in terms of caregiver burden measurement, there is substantial variation across HF and chronic illness caregiving research in how caregiver burden is defined and measured (Bastawrous, 2013). In this study, burden was primarily quantified in relation to difficulty with care tasks. Since the clinical trajectory of HF is unpredictable and characterized by periods of exacerbation followed by stretches of relative stability, HF care tasks are similarly unpredictable, and may vary independently of disease stage (Kitko et al., 2020). In future HF caregiving studies that focus on symptom appraisal and/or management, it may be beneficial to add HF symptom measures that capture the full range and severity of symptoms (such as the Heart Failure Somatic Perception Scale: Jurgens et al., 2017), HF severity measures that include objective indicators of disease progression, and care burden instruments that capture physical, social, psychological, financial, and other dimensions of care-related strain (such as the Multidimensional Care Strain Index: Stull, 1996; or the Zarit Burden Interview: Bedard et al., 2001).

Our second hypothesis – that greater severity of patient HF would be associated with elevated markers of caregiver physiological stress – was generally supported (i.e. was significantly associated with all markers of caregiver physiological stress, although at differing levels of patient functional class). In HF, examination of physiologic caregiving stress remains a substantial research gap – there are no studies of stress biomarkers in relationship to patient symptomatology or functional decline, and very limited examination of physiological stress and stress biomarkers overall, particularly in diverse samples (Kitko et al., 2020). There has been comparatively more physiological stress research conducted in other types of caregivers, primarily caregivers of persons with

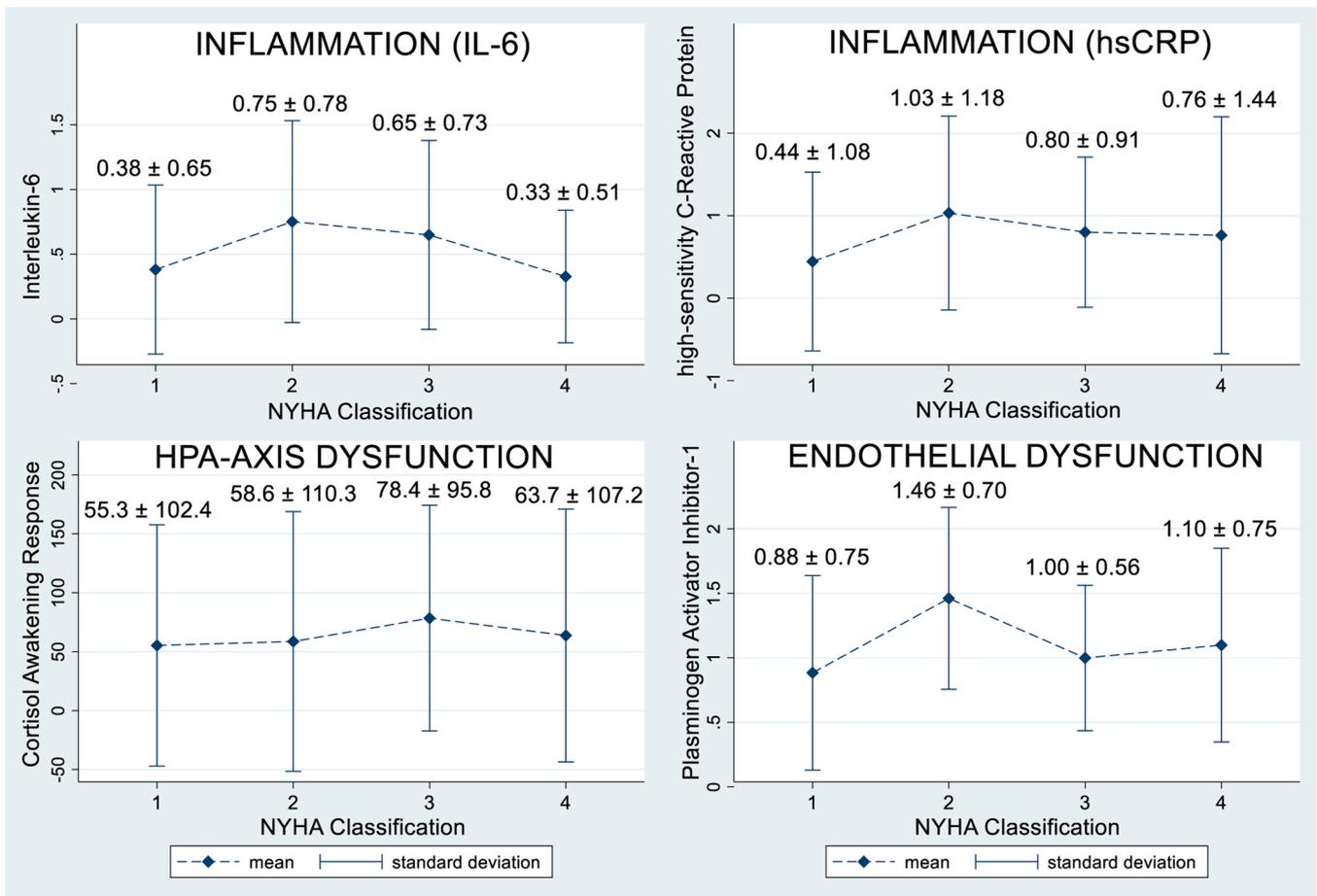


Fig. 2. Caregiver physiological stress variables (IL-6, hsCRP, PAI-1 natural log transformed) by caregiver-assessment of the care recipient’s heart failure functional classification (higher NYHA Class indicates greater severity of care recipient heart failure symptoms). Abbreviations: NYHA, New York Heart Association.

Table 2

Multiple regression results for heart failure severity as a predictor of caregiver psychological stress.

	Model 1: Caregiver Burden (Oberst)		Model 2: Depression (CESD)		Model 3: Anxiety (STAI)		Model 4: General Stress (PSS-10)	
Independent Variables	<i>b</i> ± <i>SE</i>	<i>p</i> -value	<i>b</i> ± <i>SE</i>	<i>p</i> -value	<i>b</i> ± <i>SE</i>	<i>p</i> -value	<i>b</i> ± <i>SE</i>	<i>p</i> -value
Care Recipient HF Severity^a								
Mild HF symptoms (NYHA Class II; Class I as referent)	2.33 ± 3.92	0.55	3.24 ± 3.21	0.31	8.69 ± 4.11	0.03*	3.46 ± 1.96	0.07
Marked/severe HF symptoms (NYHA Class III/IV; Class I/II as referent)	3.28 ± 2.77	0.24	2.21 ± 1.99	0.27	2.46 ± 2.64	0.35	2.71 ± 1.37	<0.05*
Caregiver Characteristics								
Age	-0.11 ± 0.15	0.47	-0.20 ± 0.10	< 0.05*	-0.43 ± 0.14	<0.01*	-0.19 ± 0.07	<0.01*
Female gender	3.16 ± 4.73	0.50	1.61 ± 3.49	0.64	1.59 ± 4.61	0.73	-0.33 ± 2.36	0.89
African American race	-0.54 ± 3.24	0.87	-1.72 ± 2.13	0.42	-6.54 ± 2.94	0.03*	-2.59 ± 1.45	0.07
Education (college or higher)	5.58 ± 2.86	<0.05*	2.42 ± 2.10	0.25	-1.35 ± 2.88	0.64	1.99 ± 1.42	0.16
Caregiving relationship (spouse/partner)	-2.50 ± 3.72	0.50	0.68 ± 2.72	0.80	2.93 ± 3.45	0.40	0.01 ± 1.72	0.99
Cohabitation (Caregiver lives with patient)	3.09 ± 4.42	0.48	1.77 ± 3.62	0.62	3.11 ± 4.23	0.46	-0.39 ± 2.34	0.87
Comorbidities ^b	0.74 ± 1.16	0.53	0.51 ± 1.02	0.62	-0.59 ± 1.03	0.57	1.31 ± 0.75	0.08

*indicates p-value < 0.05.

^aNYHA Class is backwards difference coded in this analysis (i.e., each level of the ordinal variable is coded for comparison to the mean of the prior level or combined levels).

^bCharlson Comorbidity Index.

Abbreviations: HF = Heart Failure; NYHA = New York Heart Association; b = unstandardized beta coefficient; SE = standard error; Oberst = Oberst Caregiving Burden Scale; CESD = Center for Epidemiological Studies Depression Scale; STAI = State Trait Anxiety Inventory; PSS-10 = Perceived Stress Scale 10-item version. Note: Complete case analysis. Model 1 n = 110; Model 2 n = 121; Model 3 n = 120; Model 4 n = 121.

dementia, and to a lesser degree, cancer (Allen et al., 2017; Park et al., 2018; Roth et al., 2019). Most of these studies compare physiological markers (primarily markers of inflammation and/or HPA-axis dysfunction) between caregivers and non-caregiving controls, or test associations between subjective stress and physiological markers within

caregivers. For example, there are several prior caregiving studies examining IL-6 and CRP, where CRP and IL-6 have both been associated with caregiving status (Allen et al., 2017; Park et al., 2018). However overall, evidence that caregiving status or caregiver stress is related to markers of inflammation or HPA-axis dysfunction is mixed, with

Table 3
Multiple regression results for heart failure severity as a predictor of caregiver physiological stress.

Independent Variables/Care Recipient HF Severity ^a	Model 1: Inflammation (IL-6)		Model 2: Inflammation (hsCRP)		Model 3: HPA-Axis Dysfunction (CAR >75%)		Model 4: Endothelial Dysfunction (PAI-1)	
	b ± SE	p-value	b ± SE	p-value	OR ± SE	p-value	b ± SE	p-value
Mild HF symptoms (NYHA Class II; Class I as referent)	0.42 ± 0.16	< 0.01 *	0.67 ± 0.27	0.01*	1.80 ± 1.25	0.40	0.82 ± 0.19	<0.01*
Marked/severe HF symptoms (NYHA Class III/IV; Class I/II as referent)	0.07 ± 0.11	0.52	0.00 ± 0.19	0.98	2.84 ± 1.36	0.03*	-0.19 ± 0.13	0.16
Caregiver Characteristics								
Age	0.00 ± 0.01	0.51	-0.01 ± 0.01	0.55	1.07 ± 0.03	<0.01*	0.00 ± 0.01	0.56
Female gender	-0.04 ± 0.20	0.82	0.87 ± 0.34	0.01*	-**	-	0.09 ± 0.24	0.72
African American race	0.07 ± 0.12	0.54	0.17 ± 0.21	0.40	0.81 ± 0.41	0.68	-0.21 ± 0.15	0.16
Education (college or higher)	-0.18 ± 0.12	0.14	0.50 ± 0.20	<0.01*	0.46 ± 0.23	0.11	-0.03 ± 0.14	0.86
Caregiving relationship (spouse/partner)	0.21 ± 0.14	0.15	0.24 ± 0.25	0.33	0.57 ± 0.35	0.36	0.18 ± 0.18	0.30
Cohabitation (Caregiver lives with patient)	-0.34 ± 0.18	0.06	-0.31 ± 0.30	0.30	1.59 ± 1.20	0.54	-0.06 ± 0.22	0.80
Comorbidities ^b	-0.12 ± 0.05	<0.01*	-0.12 ± 0.08	0.13	0.89 ± 0.18	0.54	-0.09 ± 0.06	0.09
Adiposity (waist-hip ratio)	0.97 ± 0.73	0.18	1.19 ± 1.30	0.36	0.58 ± 1.79	0.86	-0.46 ± 0.91	0.62
Cardiovascular Medications ^c	0.44 ± 0.13	<0.01*	0.51 ± 0.22	0.02*	0.63 ± 0.33	0.38	0.01 ± 0.16	0.93
Selective Serotonin Reuptake Inhibitors	0.05 ± 0.21	0.80	-0.53 ± 0.36	0.14	0.55 ± 0.49	0.50	-0.45 ± 0.26	0.08
Sleep Quality ^d	-0.03 ± 0.01	0.03*	0.00 ± 0.02	0.94	1.03 ± 0.06	0.60	0.00 ± 0.02	0.76
Pain ^e	-	-	-	-	1.04 ± 0.03	0.11	-	-

*indicates p-value <0.05.

**male gendered participants omitted from the cortisol model due to lack of variability in outcome by male gender (i.e. no males in sample had cortisol awakening response >75%).

^aNYHA Class is backwards difference coded in this analysis (i.e., each level of the ordinal variable is coded for comparison to the mean of the prior level or combined levels).

^bCharlson Comorbidity Index.

^cTaking aspirin, antihypertensives, or statins.

^dPittsburgh Sleep Quality Index.

^eSF-36 Bodily Pain scale.

Abbreviations: HF = Heart Failure; NYHA = New York Heart Association; b = unstandardized beta coefficient; OR = odds ratio; SE = standard error; IL-6 = interleukin 6; hsCRP = high-sensitivity C-reactive protein; CAR = salivary cortisol awakening response; PAI-1 = serum plasminogen activator inhibitor-1.

Note: Complete case analysis. Model 1 n = 109; Model 2 n = 112; Model 3 n = 104; Model 4 n = 113.

substantial variability across studies and small effect sizes when significant relationships are identified (Potier et al., 2018; Roth et al., 2019). Further, across conditions, inclusion of underrepresented racial and ethnic minority caregivers remains limited.

Our examination of patient HF severity in relation to caregiver markers of inflammation, HPA-axis function, and hypercoagulation is therefore novel in the caregiving literature in HF and more broadly. While our hypothesis that caregiver markers would increase with patient symptoms was supported, our analysis also found that this relationship is most likely non-linear, and also differs across stress markers. Namely, the transition to caring for a symptomatic HF patient (Class II versus Class I) was the point at which our diverse caregiving sample had significantly higher markers of inflammation and endothelial dysfunction, while HPA-axis dysfunction was only significantly associated with caring for a patient with more severe HF (Class III/IV versus I/II). Interestingly, markers of inflammation or hypercoagulation were not significantly higher (or lower) when comparing caregiving for a patient with more severe symptoms to caring for a patient with mild or no symptoms (i.e. no difference in inflammatory or hypercoagulability markers in caregivers caring for a Class III/IV patient as compared to those caring for a Class I/II patient).

This suggests that the emergence of HF symptoms – either as a function of the symptoms themselves or some other aspect of the disease/caregiving experience that changes with the transition in functional status to symptomatic HF – may be a key point in the trajectory of caregiver stress and health. Though our results should be considered exploratory, elevated markers of inflammation and hypercoagulation may be particularly concerning when observed in caregivers of patients at early stages of symptomatic disease, given that the patient commonly remains symptomatic as their HF progresses over years or decades. In short, we cannot assume that a caregiver of an early-stage HF patient is at lower physiological health risk related to caregiving than a late-stage patient. Rather, exposure to risk may begin much earlier than expected and persist over extended periods, potentially compounding known risks

for morbidity and mortality related to caregiving stress and chronic inflammation (Furman et al., 2019; Schulz et al., 2020). These findings have important implications, given that CRP in particular has been shown to predict cardiovascular events and mortality in a dose-response fashion in multiple large epidemiological studies (Ridker, 2007).

Our findings have implications for research. Perhaps foremost, there is a dearth of longitudinal research in HF caregiving overall (Kitko et al., 2020). Our findings provide further evidence that research on the HF caregiving trajectory is needed, and that physiological markers of caregiving stress may be valuable to include across that trajectory, even at early stages (Kitko et al., 2020; Park et al., 2018; Roth et al., 2019). HF is a notoriously heterogeneous disease, both in terms of patient experience/prognosis, as well as caregiver experience and tasks. The caregiving time and activities required in HF caregiving are highly variable and depend on a number of factors, which include not only the severity and stability of HF but also the presence of comorbidities, impairments to physical and/or cognitive function, complexity of the treatment regimen, and other situational aspects (Kitko et al., 2020). In general, however, caregiving at the initial diagnosis of HF typically involves assisting the patient with medication management and dietary modifications (e.g. heart-healthy diet and sodium restriction), learning HF self-care behaviors and how to monitor for exacerbations, navigating the health system and coordinating care, and providing psychosocial support and support with basic and instrumental activities of daily living (depending on the patient’s level of function at the time of diagnosis). As the disease progresses, treatment regimen complexity increases and HF self-care efforts become more intense as patients and caregivers must also intensively monitor and manage increasing symptoms. Clinic appointments, medication changes, and hospitalizations become more frequent, and the patient’s need for psychosocial support and assistance with activities of daily living intensifies, particularly in the advanced stages, when caregivers often need to manage medical equipment and nursing tasks associated with advanced therapies (Kitko et al., 2020). Perhaps most importantly, the progression of HF is punctuated by

substantial instability and uncertainty, and there are fewer caregiving resources/supports for HF caregivers in comparison to caregivers of persons with other chronic diseases (e.g. dementia, cancer) from which the majority of the physiologic caregiving stress literature is derived. In particular, there is a substantial gap in our understanding of which aspects of HF caregiving, and at what points in the trajectory, place caregivers at the greatest psychological and physiological health risk. In studying the co-evolution of patient disease progression alongside caregiver stress, it may be helpful to consider approaches designed to model shared experience (e.g. dyadic methods), and that are flexible to non-linear trajectories, given that neither patient disease progression nor intensity of clinical or home management is linear (Allen et al., 2012; Kitko et al., 2020). It may also be useful to consider HF caregiving stress in terms of transitions between important phases where new uncertainties arise, or new care responsibilities are added, such as symptom management or care associated with advanced therapies.

Our findings also have potential clinical implications. Prior research across caregiving contexts suggests that caregivers of patients with more severe illness may need the most support (Schulz et al., 2020), which generally aligns with our findings. However, our findings of elevated psychological and physiological stress related to caregiving for a Class II (mildly symptomatic) versus Class I (asymptomatic) HF patient would suggest that quantifiable health risks for HF caregivers – both psychological and physiological – may arise earlier in the trajectory of care recipient disease than previously considered. It may therefore be reasonable to consider earlier clinical assessment and referral to caregiving services/supports for caregivers of persons with HF who have only recently become symptomatic, or are in stable, early-stage HF. It is important to remember that the transition from Class I to Class II HF adds new tasks and complexity to the caregiving role, as symptom recognition and response – critical for maintaining clinical stability – are notoriously difficult for both patients and caregivers (Riegel et al., 2015). It is also reasonable to assess caregiver stress in multiple ways, as we found elevations in general stress and anxiety in relation to caregiving for a symptomatic (i.e. Class II or higher) HF patient, without elevations in caregiving-specific stress (i.e. care strain/burden). This may be particularly salient if the caregiver does not identify with the role of “caregiver,” or does not consider their support of their loved one to be “caregiving,” but rather a function of normal family roles (Knowles et al., 2016).

This study is not without limitations, the foremost of which is the measurement of HF disease severity. As a measure of functional status in HF, NYHA Classification is the clinical standard. However, this measure is usually evaluated by clinicians (rather than caregivers), and as a research measure of disease severity and symptom burden, it does not have the precision of other instruments that are commonly used to quantify HF symptoms. This is notable because the HF symptom experience (both the types of symptoms experienced and their relative severity) can be different across patients, and likely create different experiences of stress for family caregivers. Our study suggests that HF patient functional status (as demonstrated by their overall symptoms) is likely important in relation to caregiver stress. However, future studies examining this phenomena would benefit from using more precise measures of patient HF symptoms (e.g. Heart Failure Somatic Perception Scale: Jurgens et al., 2017) alongside additional subjective and objective measures of HF disease severity. Additional objective measures of HF disease severity would also overcome another clear limitation of this study, namely, that caregivers reported on both HF disease status and their own distress, which may contribute to confounding. Second, this was a secondary analysis of cross-sectional baseline data from an exercise intervention, and the inclusion/exclusion criteria related to the intervention (i.e. able to participate in low impact walking and strength training safely) yielded a sample that was younger than the broader population of HF caregivers, and relatively healthy. This sample also had relatively few male caregivers, making it impractical to consider gender in relation to outcomes, however, given the differences in caregiving

experiences by gender observed in other studies, as well as numeric differences on outcome variables in the present study (Appendix 2), it would be valuable in future studies to have balanced gender samples. The sample likewise had fewer caregivers for NYHA Class IV patients (the most severely ill) as compared to Classes I-III. This study also did not include some additional data that would have strengthened the analysis, including measurement of sleep the night immediately prior to biomarker collection (which has well-documented effects on cortisol as well as IL-6), a precise measure of caregiving hours per week, and more clarity on caregiving relationships that were not spousal or adult-child.

The present study also has a number of strengths, including its examination of multiple measures of both subjective and physiologic stress, and a diverse sample of adequate size to include most common confounders in our models. However, there is still the possibility that some models in our analysis may suffer from overfitting, and replication in larger samples would be valuable. Substantial representation of African American caregivers is a particular strength, given the comparative lack of studies of physiologic stress in African American caregivers across patient conditions, not just HF. However, we did not examine race as a moderator, which is an important limitation and would be valuable to include in an analysis when a larger sample is available. The sample also included a good proportion of caregivers of asymptomatic (NYHA Class I) patients, which is unique given that many studies only examine symptomatic (Class II or greater) HF patients. Lack of representation of early-stage HF patients in many caregiving studies limits the conclusions that can be drawn about differences in experience between asymptomatic and symptomatic patients, making the present study a unique contribution to symptom science in HF caregiving.

5. Conclusions

Caregiving as an exposure condition is highly heterogeneous – not just across care recipient illnesses, but within illnesses and within individuals. It is therefore important to examine aspects of that exposure that are salient in understanding caregiver risk and designing appropriate interventions. HF severity, which is primarily characterized by progressive and distressing symptoms, is a central aspect of families' experience of HF at home, as well as clinical management. In the present study, most associations between patient HF severity and caregiver stress seemed to emerge at relatively early stages of HF functional limitations (i.e. Class II), while others emerged when the patient's HF was more severe. While our findings support the broad hypothesis that patient symptoms are significantly associated with risk to caregiver psychological and physiological health, more work is needed to better understand this risk and the variability around it. In particular, understanding which aspects of patients' HF are most stressful for caregivers at what point in the HF trajectory, and which modifiable caregiver characteristics are most predictive of resilience to stress, are needed to inform targets and timing of much-needed caregiver interventions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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responsibility of the authors and does not necessarily represent the official views of the funders.

Appendix 1. Correlation table for continuous variables used in analysis

Age	-														
Comorbidities	0.18*	-													
Adiposity	0.09	0.09	-												
Sleep Quality	-0.08	0.00	0.01	-											
Pain	-0.26*	-0.23*	-0.02	-0.32*	-										
Patient NYHA Class	-0.02	0.14	0.08	0.08	-0.15	-									
Caregiver Burden	-0.10	0.12	0.10	0.24*	-0.19*	0.13	-								
Depression	-0.16	0.00	-0.09	0.52*	-0.27*	0.13	0.40*	-							
Anxiety	-0.20*	-0.07	-0.01	0.37*	-0.22*	0.16	0.30*	0.70*	-						
General Stress	-0.23*	0.09	-0.08	0.40*	-0.26*	0.17	0.42*	0.71*	0.67*	-					
Inflammation (IL-6)	0.14	-0.13	0.14	-0.04	-0.10	0.12	-0.01	-0.04	-0.03	-0.06	-				
Inflammation (hsCRP)	-0.03	-0.04	0.09	0.08	-0.03	0.05	0.19*	0.12	0.08	0.11	0.32*	-			
HPA-Axis Dysfunction (CAR)	0.16	0.01	-0.10	-0.08	-0.02	0.07	0.00	-0.01	0.08	-0.08	-0.05	-0.15	-		
Endothelial Dysfunction (PAI-1)	-0.07	-0.09	0.00	0.09	-0.02	-0.03	0.12	0.08	0.11	0.08	0.06	0.20*	-0.05	-	
	Age	Comorbidities	Adiposity	Sleep Quality	Pain	Patient NYHA Class	Caregiver Burden	Depression	Anxiety	General Stress	IL-6	hsCRP	CAR	PAI-1	

Pearson's correlations, values in cells are Pearson's r.

*p-value < 0.05.

Appendix 2. Outcome comparisons by gender

	Full sample (n = 125)	Men (n = 10)	Women (n = 115)	Comparison
Outcome	Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)	p-value ^a
Caregiver Burden	33.29 ± 14.40	29.30 ± 10.22	33.68 ± 14.73	p = 0.36
Depression	15.08 ± 10.21	12.17 ± 10.99	15.33 ± 10.15	p = 0.35
Anxiety	40.94 ± 14.78	36.23 ± 11.61	41.35 ± 15.00	p = 0.30
General Stress	17.10 ± 7.32	15.2 ± 6.75	17.26 ± 7.37	p = 0.40
Inflammation (IL-6)	2.13 ± 1.71	2.26 ± 1.77	2.12 ± 1.71	p = 0.79
Inflammation (hsCRP)	3.25 ± 3.34	2.11 ± 3.81	3.36 ± 3.29	p = 0.26
HPA-Axis Dysfunction ^b (CAR >75%)	43 (34.68%)	0 (0%)	43 (37.72%)	p = 0.02
Endothelial Dysfunction (PAI-1)	3.80 ± 2.86	2.78 ± 1.79	3.89 ± 2.92	p = 0.24

^ap-value is for independent samples t-test when outcome is continuous (two-tailed); when outcome is binary, p-value is for chi-square test.

^bBinary variable: Cortisol awakening response greater than 75%.

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